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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,622	08/29/2003	Yawei Ni	04137.0003U3	1025

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ATLANTA, GA 30309-3915

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,622	NI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,9-31,33,35-41,53,55-62,65-71 and 74-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 9-31, 33, 35-41, 53, 55-62, 65-71, and 74-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claims 1, 2, 9-31, 33, 35-41, 53, 55-62, 65-71, and 74-112 remain pending and are under consideration in this Office Action.

This application is a continuation in part of 09/795,897, now US 6,777,000. However, the instant claims require a powder comprising nanoparticles or microparticles that can pass through a sieve having an opening size of about 250 microns in diameter. US 6,777,000 does not support this limitation, so the effective filing date of the instant claims is considered to be 8/29/03.

Rejections/objections not reiterated from the previous action are withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Baichwal et al (US Patent 5,612,053) in view of Watts et al (US 6,310,089) and Ni et al (US Patent 5,929,051).

Baichwal taught dry powdered compositions for controlled release of drugs by inhalation, and methods of use to deliver the drugs. See column 2, lines 40-45. The dry powdered compositions comprised polysaccharides such as alginates or carrageenans, as well as a cross linking agent such as divalent metal cations, e.g. calcium chloride. See abstract; and column 6, lines 16-24 and 44-59. In various embodiments, the size of the powder particles ranges from 0.1 to 10 microns, 2 to 10 microns, 63 to125 microns, and 45 to 355 microns. See column 5, lines 30-45. The composition can be prepared as a powder by dissolving a drug and polysaccharide particles, allowing them to contact each other in solution, drying the solution to form a solid, and milling to form particles of the appropriate size. See column 8, line 4 to column 9, line 67, especially column 8 lines 51-67, and column 9, lines 1-15 and 27-59. Absent evidence to the contrary, this results in contact between molecules of polysaccharide and molecules of drug, resulting in mixing on the molecular level. With regard to instant claim 2, note that the compositions can comprise more than one type of polysaccharide (column 5, lines 57-59). The compositions are delivered to regions of the body comprising fluids such as the respiratory tract (see column 5, lines 45-52). The drug can be any of a wide variety of drugs including polypeptides and peptides, see column 10, lines 1-8 and 62-65.

Pharmaceutically acceptable excipients and fillers are included in the composition, see column 7, lines 16-55.

Baichwal did not teach a pectin.

Watts taught powders for inhalation comprising powdered polysaccharide microspheres including alginates and pectin, among others.

Ni taught that a calcium-induced gel-forming aloe pectin (AP 97-1) having a molecular weight of 1.36 X 10^6 Da, 91% (w/w) galacturonic acid, a degree of methylation of 4.4%, 10.3% (mole/mole) rhamnose, and 0.8% (mole/mole) 3-methoxy rhamnose, was suitable for the controlled release of a physiologically active agent to an animal. See column 5, lines 55-58, Table 10 at columns 19 and 20, column 27, lines 25-67, Figs. 5a-c, and Table 17 at columns 31 and 32. Ni also taught that the pectin was useful for delivering vaccines to mucosal surfaces of animals. See column 5, lines 55-58.

It would have been obvious to one of ordinary skill in the art at the tie of the invention to use a pectin as a polysaccharide in the invention of Baichwal, because it was clear that pectins were routinely used in powdered compositions for inhalation at the time of the invention, as evidenced by Watts. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known

material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, it was clear to one of skill in the art that pectins and alginates could both be used in powdered microsphere form to deliver drugs by inhalation, so it would have been obvious to substitute one for the other in the method of Baichwal.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the pectin of Ni in the invention of Baichwal. One would have been motivated to do so because Ni taught that the pectin was suitable for controlled release of a physiologically active agent to an animal. MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Although Baichwal is silent as to whether or not the divalent metal cation is a solid phase that is distinct from the mixed polysaccharide and drug solid phase, the inclusion of the divalent cation in this phase or its addition as a separate solid phase is considered to be a matter of design choice.

Regarding claims 29, 68, 71, and 106, requiring a thickener, the polysaccharide of Baichwal is considered to be a thickener. Note that the compositions can comprise more than one type of polysaccharide (column 5, lines 57-59), and that the polysaccharides can be present in a concentration of 10-50%, typically (column 8, lines 36 and 37). Claims 37-40 and 101 are included in this rejection because it is considered to read on a method in which the solid powder of Baichwal is administered

to the lung or nasal passages, and then comes into contact with lung tissue or nasal tissue as a suspension in the extracellular or respiratory fluids. See e.g. column 5, lines 45-52.

Claims 20, 21, 75-78, 111, and 112 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Baichwal et al (US Patent 5,612,053), and Watts et al (US 6,310,089), and Ni et al (US Patent 5,929,051), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 above, and further in view of Kuo et al (US Patent 6,518,239).

The teachings of Baichwal, Watts, and Ni are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach delivery of a vaccine.

Kuo taught delivery of vaccines by inhalation of dry powders comprising a vaccine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the composition and method of Baichwal as modified by Watts and Ni to deliver a vaccine because it was clear to those of ordinary skill that the method of Baichwal could be used to deliver polypeptides by inhalation, and that polypeptide vaccines were routinely delivered by inhalation. Thus the invention as a whole was prima facie obvious.

Claims 25, 26, 90, and 91 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Baichwal et al (US Patent 5,612,053), and Watts et al (US 6,310;089), and Ni et al (US Patent 5,929,051), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110, above, and further in view of Gordon et al (US Patent 2,629,665).

The teachings of Baichwal, Watts, and Ni are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach the use of calcium phosphate.

Gordon taught that almost any calcium ion, including calcium chloride, mono-calcium phosphate, di-calcium phosphate, etc could be used to cause pectin to form a gel. See column 4, lines 6-15.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use calcium phosphate in the invention of Baichwal, as modified by Watts and Ni. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case, it was well known in the art calcium phosphate could be substituted for the

calcium chloride of Baichwal or Ni. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Claims 30, 31, 69, 70, and 107 stand rejected over Baichwal et al (US Patent 5,612,053), and Watts et al (US 6,310,089), and Ni et al (US Patent 5,929,051), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110, and further in view of Mizushima et al (US Patent 5,942,242).

The teachings of Baichwal, Watts, and Ni are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach the thickeners recited in instant claims 30, 31, 69, 70, and 107.

Mizushima taught that hydroxypropylmethylcelluloses, carboxymethylcelluloses, carboxymethylchitin, polyvinylpyrrolidone, hyaluronic acid, gelatin, and dextran were useful additives to inhalable powders because they increased adherence to the nasal mucosa. See column 5, lines 13-34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of the agents taught by Mizushima in the composition of Baichwal as modified by Watts and Ni in order to improve the adherence of the composition upon nasal administration.

Response to Arguments

Applicant's arguments, and the Declaration of Dr. Ni, filed 10/31/07 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 17-23 of the response.

Applicant argues at page 18 that none of the cited references alone or in combination taught or suggested an ungelled solid pharmaceutical composition that forms a bioadhesive gel *in situ* on application to mucosal surfaces. Applicant relies for support on the Declaration of Dr. Ni, paragraphs 12-14. Applicant raises the issue of the definition of "*in situ*" with regard to the property of gellation. Applicant and Declarant explain that what is meant by "*in situ* gellation" is the property of the claimed solid powder to form a gel, without dissolving, when contacted with nasal fluids or simulated nasal fluids. This is discussion is irrelevant to the rejection for two reasons.

First, the claims do not require "in situ" gellation as defined in Applicant's response and in the Declaration. The term does not appear in the claims. Instead the claims require the formation of a gel upon contact with a tissue or body fluid of an animal.

The second reason is that the aloe pectin of Ni (US Patent 5,929,051) has the inherent property of forming gels on contact with bodily fluids. The instant claims require a pectin having a degree of methylation of less than about 50% and the instant specification taught that aloe pectins have a degree of methylation of less than 10% and will form gels spontaneously when administered to with a degree of methylation of less than a polysaccharide gel-inducing composition comprising one or more salts of a

divalent or multivalent cation. Ni '051 clearly taught a calcium-induced gel-forming aloe pectin (AP 97-1) having a molecular eight of 1.36 X 10^6 Da, 91% (w/w) galacturonic acid, a degree of methylation of 4.4%, 10.3% (mole/mole) rhamnose, and 0.8% (mole/mole) 3-methoxy rhamnose, was suitable for the controlled release of a physiologically active agent to an animal. See column 5, lines 55-58, Table 10 at columns 19 and 20, column 27, lines 25-67, Figs. 5a-c, and Table 17 at columns 31 and 32. The instant Application taught that such non-gelled pectins will form a gel on contact with body fluids. See page 32, line 19 to page 33, line 10. Thus these pectins have the inherent property of forming a gel in situ in an animal in response to contact with bodily fluids.

At page 19 Applicant asserts that the claimed powder compositions show the remarkable but unexpected property of forming gels, rather than dissolving, when placed in simulated nasal fluids comprising about 5 mM Ca^{2+} salts. Applicant relies for support on the Declaration of Dr. Ni at paragraphs 14 and 16. However, gel formation is not described in the Declaration of Dr. Ni as "unexpected". Further, the prior art (Ni ('051)) indicated that aloe pectins formed gels in the presence of aqueous solutions of 1-2 mM $CaCl_2$, and the instant specification at page 42, lines 17-18 and page 44, lines 1-14 indicated that it was known in the prior art that nasal fluids contain Ca ions at a concentration greater than this range. Therefore it is not clear that gel formation by aloe pectin powders in vivo would be unexpected.

At page 19 Applicant argues that the gelled compositions showed delayed release characteristics in aqueous media compared to non-gelled compositions. There

is no evidence of record to indicate that this is unexpected. One of skill would generally expect diffusion to be inversely related with the pore size of a gel, such that diffusion would be greatest at infinite pore size, i.e. in the absence of a gel.

Applicant argues at pages 19 and 20 that the claimed compositions possess the unexpected property that they are thermally and storage stable, relying for support on the Declaration of Dr. Ni at paragraph 15 and Table 3. MPEP 716.02(b) indicates that evidence relied upon to support an allegation of unexpected results should establish that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. The statistical significance of the results presented in Table 3 is unknown because there is no statistical analysis. Furthermore, the practical significance is also unclear since The HA activity in the absence of pectin is equally stable to that in the presence of pectin. The significance of the difference in activity is unclear due to a lack of statistical analysis. It is also unclear what units of activity are used to express the data, although it may be that Applicant determined the number of 2-fold dilutions necessary to arrive at a sample that contains one 1 hemagglutinating unit. If that is the case, then it is not clear that a difference of only a single dilution is of practical significance. Accordingly the data in Table 3 are not supportive of unexpected results. Note also that the results are not commensurate in scope with the claims because the claims are not limited to compositions comprising whole virion antigens as used in the experiment. Instead, they include compositions comprising live cells that may not necessarily be used for antigen presentation, or be stored indefinitely in dry powder form.

At page 20 Applicant asserts that the claimed compositions form thin gel sheets when applied to the nasal surfaces of rats, and that this is highly unexpected. This gel formation is not described in the Declaration of Dr. Ni as unexpected. As discussed above, Ni ('051) indicated that pectins formed gels in the presence of aqueous solutions of 1-2 mM $CaCl_2$, and the instant specification at page 42, lines 17-18 and page 44, lines 1-14 indicated that it was known in the prior art that nasal fluids contain Ca ions at concentrations at or above that range. Therefore it is not clear that gel formation nasal passages would be unexpected. Applicant asserts that the persistence of the gels stands in contrast to the clearance time for normal materials on human nasal mucosal surfaces. This assertion is supported at paragraph 16 of the Declaration, which cites Exhibit F. Exhibit F indicates that the clearance time for particulates is estimated to be 12-15 minutes with times greater than 30 minutes being abnormal. Exhibit F also indicates that the size and weight of the particle (within reasonable limits) do not significantly affect the clearance time. Representative particles include a "small inert particle, tagged with Technetium" and saccharine particles. There is nothing in the exhibit that would indicate that a sheet of gel formed in the nasal passage is a particle of a size and weight that would be expected to clear within 12-15 minutes. Accordingly it is not clear that the 5 hour persistence of the gel in the nasal passages is unexpected.

Also at page 20. Applicant asserts that animal testing showed that large increases in immune response correlated with the inclusion of pectins in nasal powder vaccines. Applicant relies for support on the Declaration at paragraph 19-22 and Tables 4 and 5. Dr. Ni declares that the results in Table 4 showed the presence of pectin

significantly and unexpectedly increased the immune response ($p< 0.05$). However, it is unclear how this level of significance was arrived at. It is also unclear exactly what the data represent. The title of the table states "HAI titers [GMT (SD)]". This could indicate that the data represented in the Table by bold face numerals are mean titers, and that the parenthetical numerals represent standard deviations. If this is the case, then the results would appear to show insignificant differences. It is worth noting that statistically significant differences are designated with an asterisk in Table 5, but there is no such designation in Table 4. Table 5 represents a comparison of different pectin concentrations without any no-pectin control. Data for 0.5% and 1.0% pectin are presented in both tables, but are not reproducible, particularly at four weeks post inoculation. Accordingly comparisons between the no-pectin control of Table 4, and the data in Table 5 are not warranted, and Applicant's arguments and Declaration are not persuasive regarding any significant increase in immune response as a result of the inclusion of aloe pectins.

At page 21 of the response Applicant argues that the claimed compositions meet an long felt but unmet need in the art, based on their unexpectedly superior results in terms of thermal and storage stability, in situ gellation, and unexpectedly strong immune responses. This is unpersuasive because, as discussed above, Applicant has not met the burden of establishing unexpected results.

In the paragraph bridging pages 22 and 23 of the response, Applicant indicates that a passage in Baichwal relied upon the Examiner to support an assertion that the compositions of Baichwal absorb water and form gels does not support this assertion.

The Examiner agrees. However, as discussed above, the aloe pectins of Ni ('051) would inherently form gels, it is not clear that this was unexpected because Ni ('051) taught that aloe pectins gelled at Ca^{2+} concentrations recognized in the prior art to be found in nasal secretions, and also because it is not clear that the slower clearance rates for gels (compared to particles) would be unexpected.

At the paragraph bridging pages 22 and 23 of the response Applicant argues essentially that prior art pectins do not have the gellation characteristics of the pectins of the claimed invention. This is unpersuasive because Applicant has not distinguished between the prior art aloe pectins of Ni ('051) and the instantly claimed pectins.

For these reasons the rejections are maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-70 of U.S. Patent No. 5,929,051 in view of Baichwal et al (US Patent 5,612,053) and Watts et al (US 6,310,089).

Ni claimed a calcium-induced gel-forming aloe pectin (AP 97-1) having a molecular weight of 1.36 X 10^6 Da, 91% (w/w) galacturonic acid, a degree of methylation of 4.4%, 10.3% (mole/mole) rhamnose, and 0.8% (mole/mole) 3-methoxy rhamnose, that was suitable for the controlled release of a physiologically active agent to an animal, and methods of making the pectin. See column 5, lines 55-58, Table 10 at columns 19 and 20, column 27, lines 25-67, Figs. 5a-c, and Table 17 at columns 31 and 32. Ni also taught that the pectin was useful for delivering vaccines to mucosal surfaces of animals. See column 5, lines 55-58.

Baichwal taught dry powdered compositions for controlled release of drugs by inhalation, and methods of use to deliver the drugs. See column 2, lines 40-45. The dry powdered compositions comprised polysaccharides such as alginates or carrageenans, as well as a cross linking agent such as divalent metal cations, e.g. calcium chloride. See abstract; and column 6, lines 16-24 and 44-59. In various embodiments, the size of the powder particles ranges from 0.1 to 10 microns, 2 to 10 microns, 63 to125 microns, and 45 to 355 microns. See column 5, lines 30-45. The composition can be prepared as a powder by dissolving a drug and polysaccharide particles, allowing them to contact

each other in solution, drying the solution to form a solid, and milling to form particles of the appropriate size. See column 8, line 4 to column 9, line 67, especially column 8 lines 51-67, and column 9, lines 1-15 and 27-59. Absent evidence to the contrary, this results in contact between molecules of polysaccharide and molecules of drug, resulting in mixing on the molecular level. With regard to instant claim 2, note that the compositions can comprise more than one type of polysaccharide (column 5, lines 57-59). The compositions are delivered to regions of the body comprising fluids such as the respiratory tract (see column 5, lines 45-52). The drug can be any of a wide variety of drugs including polypeptides and peptides, see column 10, lines 1-8 and 62-65. Pharmaceutically acceptable excipients and fillers are included in the composition, see column 7, lines 16-55.

Watts taught powders for inhalation comprising powdered polysaccharide microspheres including alginates and pectin, among others.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the pectin of Ni as a polysaccharide in the invention of Baichwal, because it was clear that pectins were routinely used in powdered compositions for inhalation at the time of the invention, as evidenced by Watts. One would have been motivated to use the pectin of Ni because Ni taught that the pectin was suitable for controlled release of a physiologically active agent to an animal. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component

or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, it was clear to one of skill in the art that pectins and alginates could both be used in powdered microsphere form to deliver drugs by inhalation, so it would have been obvious to substitute one for the other in the method of Baichwal.

Although Baichwal is silent as to whether or not the divalent metal cation is a solid phase that is distinct from the mixed polysaccharide and drug solid phase, the inclusion of the divalent cation in this phase or its addition as a separate solid phase is considered to be a matter of design choice.

Regarding claims 29, 68, 71, and 106, requiring a thickener, the polysaccharide of Baichwal is considered to be a thickener. Note that the compositions can comprise more than one type of polysaccharide (column 5, lines 57-59), and that the polysaccharides can be present in a concentration of 10-50%, typically (column 8, lines 36 and 37). Claims 37-40 and 101 are included in this rejection because they are considered to read on a method in which the solid powder of Baichwal is administered to the lung or nasal passages, and then comes into contact with lung tissue or nasal tissue as a suspension in the extracellular or respiratory fluids. See e.g. column 5, lines 45-52.

Claims 20, 21, 75-78, 111, and 112 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-70 of U.S. Patent No. 5,929,051, Baichwal et al (US Patent 5,612,053) and Watts et al (US 6,310,089), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 above, and further in view of Kuo et al (US Patent 6,518,239).

The teachings of Ni, Baichwal, and Watts are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach delivery of a vaccine.

Kuo taught delivery of vaccines by inhalation of dry powders comprising a vaccine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the composition and method of Ni, as modified by Baichwal and Watts to deliver a vaccine because it was clear to those of ordinary skill that the method of Baichwal could be used to deliver polypeptides by inhalation, and that polypeptide vaccines were routinely delivered by inhalation. Thus the invention as a whole was prima facie obvious.

Claims 25, 26, 90, and 91 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-70 of U.S.

Patent No. 5,929,051, Baichwal et al (US Patent 5,612,053) and Watts et al (US 6,310,089), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 above, and further in view of Gordon et al (US Patent 2,629,665).

The teachings of Ni, Baichwal, and Watts are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach the use of calcium phosphate.

Gordon taught that almost any calcium ion, including calcium chloride, mono-calcium phosphate, di-calcium phosphate, etc could be used to cause pectin to form a gel. See column 4, lines 6-15.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use calcium phosphate in the invention of Ni, as modified by Baichwal and Watts. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case, it was well known in the art calcium phosphate could be substituted for the calcium chloride of Baichwal or Ni. Furthermore, MPEP 2144.07 indicates that the

selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Claims 30, 31, 69, 70, and 107 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-70 of U.S. Patent No. 5,929,051, Baichwal et al (US Patent 5,612,053) and Watts et al (US 6,310,089), as applied to claims 1, 2, 9-19, 22-24, 27-29, 33, 35-41, 53, 55-62, 65-68, 71, 74, 79-89, 92-106, and 108-110 above, and further in view of Mizushima et al (US Patent 5,942,242).

The teachings of Ni, Baichwal, and Watts are discussed above and can be combined to render obvious compositions comprising a pectin, a drug, and divalent or multivalent metal cation, wherein the composition is in the form of a powder of particles less than 250 microns in diameter.

The cited references did not teach the thickeners recited in instant claims 30, 31, 69, 70, and 107.

Mizushima taught that hydroxypropylmethylcelluloses, carboxymethylcelluloses, carboxymethylchitin, polyvinylpyrrolidone, hyaluronic acid, gelatin, and dextran were useful additives to inhalable powders because they increased adherence to the nasal mucosa. See column 5, lines 13-34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of the agents taught by Mizushima in the composition of Ni, as

modified by Baichwal and Watts in order to improve the adherence of the composition upon nasal administration.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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